NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA221; Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura and TA293; Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura

Original publication date:	TA221 April 2011; updated May 2014 TA293 July 2013
Review date	N/A – TA221 and TA293 were both added to the static list in May 2014
Existing recommendations:	Optimised To see the complete existing recommendations and the original remit for TA221 and TA293, see Appendix A.

1. Proposal

The wording of the guidance should be amended without the need for a full review, and the guidance should be re-issued and transferred to the static list.

2. Rationale

The marketing authorisations for both romiplostim and eltrombopag have been extended to include patients who have not had splenectomy, and children. The change with respect to prior splenectomy can be addressed by an amendment to the recommendation wording. A review is not needed because the existing recommendation is based on evidence for both patients who had and had not had splenectomy, and any new evidence supports the efficacy of the drugs regardless of whether patients have had a splenectomy.

With regards to the license extension to children aged 1 year and over, this population already has access to these technologies through the NHS England policy for "Commissioning Medicines for Children in Specialised Services". This policy advises that, provided specific criteria are met, NHS England will fund medicines for children within a specialised service that are recommended by a NICE technology appraisal.

The recommendations in TA221 and TA293 are optimised, that is, the treatments are only recommended for people with severe disease and a high risk of bleeding that needs frequent courses of rescue therapies, which the marketing authorisation does not specify. However, the clinical advice in these appraisals was that active

treatment would only be considered for this group of patients, in which most benefit was expected. There is no evidence that this has changed.

No new evidence has been identified that could be expected to lead to a change in the recommendations. Therefore, it is proposed that a full review of these appraisals is not needed, but the wording of the recommendations should be updated to reflect the license extension to patients who have not had a splenectomy.

3. Summary of new evidence and implications for review

The new evidence comprises longer term data on the safety and efficacy of romiplostim and eltrombopag, which would only strengthen the committee's original conclusions. In addition, the new evidence supports the efficacy of both drugs in both patients who have had a splenectomy and those who have not, and so evidence in patients who have had a splenectomy can be generalised to patients who have not. There are some studies showing a higher response rate in patients who have not had a splenectomy, which would make the drugs more cost-effective in this population. The uncertainties in TA293 related to the relative effectiveness of romiplostim and eltrombopag, and there is no new evidence to address this.

Overall, there is no new evidence likely to lead to change in the recommendations of the original guidance, but there is evidence to support extending the recommendations to include all people who have not had a splenectomy, and not just those for whom surgery is contraindicated, as per the current wording. Reference to splenectomy will be removed from the recommendation wording so that it is line with the current marketing authorisation, as follows:

Romiplostim is recommended as an option for treating adults with chronic immune (idiopathic) thrombocytopenic purpura, ~~within its marketing authorisation (that is, in adults who have had a splenectomy and whose condition is refractory to other treatments, or as a second-line treatment in adults who have not had a splenectomy because surgery is contraindicated),~~ only if:

- their condition is refractory to standard active treatments and rescue therapies, or
- they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies

Eltrombopag is recommended as an option for treating adults with chronic immune (idiopathic) thrombocytopenic purpura, ~~within its marketing authorisation (that is, in adults who have had a splenectomy and whose condition is refractory to other treatments, or as a second-line treatment in adults who have not had a splenectomy because surgery is contraindicated),~~ only if:

- their condition is refractory to standard active treatments and rescue therapies, **or**
- they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies

Has there been any change to the price of the technology(ies) since the guidance was published?

There has not been any change to the price of the technologies.

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

The marketing authorisations for both romiplostim and eltrombopag were extended in 2016 to include patients who had not had a splenectomy (including those without a contraindication to surgery). In TA221 and TA293 clinical and cost effectiveness was shown for both patients who had a splenectomy and those who had not, and the new evidence supports the efficacy of both drugs in both groups of patients. The extensions to the marketing authorisations therefore do not affect the committee's conclusions on clinical and cost-effectiveness, although the wording of the recommendations should be amended to reflect the current marketing authorisation with respect to splenectomy.

The marketing authorisations have also been extended to include children aged 1 year and over (eltrombopag in 2016 and romiplostim in 2018). This population already has access to these technologies through the NHS England policy for "Commissioning Medicines for Children in Specialised Services". This policy advises that, provided specific criteria are met, NHS England will fund medicines for children within a specialised service that are recommend by a NICE technology appraisal. Because of this, there would be little value in a NICE appraisal, or a review of existing guidance to include this population. However, because the cost effectiveness of the technologies in children has not been assessed, the recommendation wording cannot be changed to reflect the current marketing authorisation with respect to age.

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

The uncertainties identified in TA293 related to the relative effectiveness of eltrombopag compared with romiplostim. There are no new randomised controlled trials directly comparing eltrombopag with romiplostim. The new evidence identified comprises more data (including longer term) confirming the safety and efficacy of romiplostim and eltrombopag which would only strengthen the conclusions of the current guidance. TA293 included a recommendation that research should be carried out to directly compare eltrombopag with non-thrombopoietin receptor agonist treatments. No new evidence has been identified that addresses this recommendation.

Furthermore, the evidence base for eltrombopag and romiplostim is unlikely to change substantially in the near future because idiopathic thrombocytopenic purpura is a rare and heterogeneous condition, which makes conducting comparative trials with these drugs difficult.

There is evidence addressing the efficacy of romiplostim and eltrombopag in children, which was not considered in the original appraisals because the marketing authorisations did not include children at that time. However, as

previously discussed, this population already has access to these technologies through the NHS England policy for "Commissioning Medicines for Children in Specialised Services". Because of this, there would be little value in a NICE appraisal, or a review of existing guidance to include this population.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
See Appendix C for a list of related NICE guidance.
Additional comments
Romiplostim and eltrombopag have different methods of administration (subcutaneous and oral, respectively). Clinical advice in TA293 notes that some patients would prefer a daily oral treatment while others would prefer a weekly injection, which suggests there is value in the continuing availability of both options.

The search strategy from the original assessment report was adapted and re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from January 2014 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

In TA221, the committee was aware that certain religious groups would not consent to the use of blood products, and also that idiopathic thrombocytopenic purpura might affect pre-menopausal women more than men. It also understood that romiplostim might reduce the burden of hospital admission for long hours to receive intravenous immunoglobulin, especially for people from whom it is difficult to travel to a hospital. The committee concluded that its recommendations do account for the individual needs of people to receive romiplostim, and do not make it more difficult for any particular group to access treatment with romiplostim compared with any other group.

No equality issues were raised in TA293.

GE paper sign off: **Helen Knight, 20 August 2018**

Contributors to this paper:

Information Specialist: Toni Shaw

Technical Analyst: Anna Brett

Associate Director: Melinda Goodall

Project Manager: Emily Richards

Appendix A – Information from existing guidance

5. Original remit(s)

TA221: To appraise the clinical and cost effectiveness of romiplostim within its licensed indication for the treatment of refractory chronic idiopathic (immune) thrombocytopenic purpura**.**

TA293: To appraise the clinical and cost effectiveness of eltrombopag within its licensed indication for the treatment of refractory chronic idiopathic (immune) thrombocytopenic purpura.

6. Current guidance

TA221:

1.1. Romiplostim is recommended as an option for treating adults with chronic immune (idiopathic) thrombocytopenic purpura, within its marketing authorisation (that is, in adults who have had a splenectomy and whose condition is refractory to other treatments, or as a second-line treatment in adults who have not had a splenectomy because surgery is contraindicated), only if:

- their condition is refractory to standard active treatments and rescue therapies, or
- they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies

and

- if the manufacturer makes romiplostim available with the discount agreed in the patient access scheme.

1.2. People currently receiving romiplostim whose disease does not meet the criteria in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

TA293:

1.1 Eltrombopag is recommended as an option for treating adults with chronic immune (idiopathic) thrombocytopenic purpura, within its marketing authorisation (that is, in adults who have had a splenectomy and whose condition is refractory to other treatments, or as a second-line treatment in adults who have not had a splenectomy because surgery is contraindicated), only if:

- their condition is refractory to standard active treatments and rescue therapies, **or**

- they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies

and

- the manufacturer provides eltrombopag with the discount agreed in the patient access scheme.

1.2 People currently receiving eltrombopag whose disease does not meet the criteria in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

7. Research recommendations from original guidance

TA221:

No research recommendations are made in the guidance.

TA293:

- The Committee recommends that research should be carried out to directly compare eltrombopag with non-thrombopoietin receptor agonist treatments routinely used in UK clinical practice.

- The Committee recommends research generating and analysing observational data including, but not limited to, the existing UK ITP Registry, which collects data on the long-term outcomes of patients treated with eltrombopag and romiplostim.

8. Cost information from original guidance

TA221:

"The SPC states that romiplostim is supplied in both 500 microgram and 250 microgram vials. However, only 250 microgram vials are available in the UK. Romiplostim costs £1.93 per microgram, so a 250 microgram vial costs £482 (excluding VAT; 'British national formulary' [BNF] edition 60). The cost of treatment varies depending on the patient's weight and the dosing regimen. The cost will also be affected by any waste that results from discarding any unused drug from the single use of a 250 microgram vial. The SPC states that romiplostim is a sterile but unpreserved product and therefore is intended for single use only. The annual cost of romiplostim treatment for a person weighing 80 kg would be £8020 at a dose of 1 microgram/kg weekly and £80,204 at a dose of 10 micrograms/kg weekly (assuming no waste)."

TA293:

"The 'British national formulary' (BNF; edition 64) states that the net price of a 28-tablet pack of 25 mg eltrombopag is £770 (a single 25 mg dose costs £27.50). The net price of a 28-tablet pack of 50 mg eltrombopag is £1540 (a single 50 mg

dose costs £55). The cost per patient will vary with dose adjustment and treatment duration. The manufacturer indicated that the average daily cost of eltrombopag (based on the mean dose of eltrombopag in the EXTEND study of 51.3 mg per day) is £56.43."

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the Technology Appraisals process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to a specific date or trial.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	**Yes**
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – other relevant information

1. Relevant Institute work

Published

Immune (idiopathic) thrombocytopenic purpura: rituximab (2014) NICE evidence summary of unlicensed or off-label medicines 35

In progress

N/A

2. Details of new products

N/A

3. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
TA221: Romiplostim (Nplate) "Romiplostim has a marketing authorisation 'for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)'. The marketing authorisation also states that romiplostim 'may be considered as second line treatment for adult non-splenectomised patients where surgery is contra-indicated'" "The SPC states that romiplostim is supplied in both 500 microgram and 250 microgram vials. However, only 250 microgram vials are available in the UK. Romiplostim costs £1.93 per microgram, so a 250 microgram vial costs £482 (excluding VAT; 'British national formulary' [BNF] edition 60). The cost of treatment varies depending on the patient's weight and the dosing regimen. The cost will also be affected by any waste that results from discarding any unused drug from the single use of a 250 microgram vial. The SPC states that romiplostim	The SPC says the following: "Nplate is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1)." In December 2015 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on the following changes to the indication: "Nplate is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) ~~splenectomised~~ patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1). ~~Nplate may be considered as second line treatment for adult non-splenectomised patients where surgery is contra-indicated~~." In November 2017 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
is a sterile but unpreserved product and therefore is intended for single use only. The annual cost of romiplostim treatment for a person weighing 80 kg would be £8020 at a dose of 1 microgram/kg weekly and £80,204 at a dose of 10 micrograms/kg weekly (assuming no waste)."	on the following changes to the indication: "Nplate is indicated for ~~adult~~ chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients **one year of age and older** who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1)." It still appears to be the case that romiplostim is only available in 250 microgram vials (eBNF), while the SPC also lists 500 microgram vials. The NHS indicative price for 250 micrograms is listed in eBNF (June 2018) as the same as the original TA, £482.

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
TA293: Eltrombopag (Revolade) The indication in the original guidance says the following: "Eltrombopag has a UK marketing authorisation for the treatment of adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) in patients who have had a splenectomy and whose condition is refractory to other treatments (for example, corticosteroids or intravenous immunoglobulins), and as a second-line treatment for patients who have not had a splenectomy because surgery is contraindicated. The European public assessment report states that the licence for patients who have not had a splenectomy is	In December 2015 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on the following changes to the indication: "Revolade is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) (see sections 4.2 and 5.1). ~~splenectomised~~ patients who are refractory to other treatments (e.g. corticosteroids, or immunoglobulins) ~~Revolade may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated~~."

restricted to patients for whom surgery is contraindicated. The report states that the benefit-harm balance could not be considered favourable for patients for whom a splenectomy remained a therapeutic option." In terms of price, the original guidance says: "The 'British national formulary' (BNF; edition 64) states that the net price of a 28 tablet pack of 25 mg eltrombopag is £770 (a single 25 mg dose costs £27.50). The net price of a 28 tablet pack of 50 mg eltrombopag is £1540 (a single 50 mg dose costs £55). The cost per patient will vary with dose adjustment and treatment duration. The manufacturer indicated that the average daily cost of eltrombopag (based on the mean dose of eltrombopag in the EXTEND study of 51.3 mg per day) is £56.43."	In January 2016 CHMP adopted a positive opinion on the following changes to the indication: "Revolade is indicated for ~~adult~~ chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients **aged 1 year and above** who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1)". This is the current indication. The SPC suggests a starting dose of 50mg daily for adults and children aged 6 to 17 years, or (as set out in TA293) 25mg for people "of East Asian ancestry". 25mg is also the starting dose in the SPC for children aged 1 to 5 years. The NHS indicative price in the BNF (June 18) remains the same, namely a 28 tablet pack of 25 mg eltrombopag is £770 and a 28 tablet pack of 50 mg eltrombopag is £1540. The BNF lists a 28 tablet pack of 75 mg eltrombopag as being available at £2310.

4. Registered and unpublished trials

Trial name and registration number	Details
Indirect Comparison of Efficacy of Treatments for Idiopathic Immune Thrombocytopenic Purpura - Review of Platelet Responses and Bleeding Events NCT01236014	Only enrolled 1 participant. Started August 2009, completion date October 2009. There are no results on the trial record.
Long-term Safety Study of Treatment With the Thrombopoietin Agonists Eltrombopag and Romiplostim in Patients With Primary Immune Thrombocytopenia (ITP) NCT01443351	Recruiting. Start March 2012, estimated primary completion March 2020.

Appendix D

Trial name and registration number	Details
Treatment of thromBocytopenia With EltRombopag or Intravenous Immune Globulin (IVIG) Before and DurING Invasive Procedures in Patients With Immune ThrombocytoPenia- BRIDGING ITP Study NCT01621204	Phase III, currently recruiting. Start date 2012. Estimated study completion date January 2019. Listed in the previous RPP (March 2014) which says: "The Committee recommended that research should be carried out to directly compare eltrombopag with non-thrombopoietin receptor agonist treatments routinely used in UK clinical practice. An RCT was designed to compare eltrombopag with intravenous immunoglobulin in ITP patients undergoing surgery (NCT01621204). However, no results appear to be available for this study."
A Phase II, Open-label, Prospective, Single-arm, Study to Assess Ability of Eltrombopag to Induce Sustained Remission in Subjects With ITP Who Are Refractory or Relapsed After First-line Steroids NCT03524612	Phase II, currently recruiting. Estimated start date July 2018. Estimated completion date August 2020.
Association of FC Gamma RIIIA Polymorphism and Thrombopoietin (THPO) Expression With Response to TPO Agonists in Refractory ITP and the Impact of Therapy on B and T Cells Subsets in the Patients With Mutated Genotypes NCT02877212	Phase III, currently recruiting. Start date 2016. Estimated completion date September 2017. "This clinical trial aims to investigate the association of Fc gammaRIIIA gene (V158F) genetic predisposition with treatment outcome of Immune Thrombocytopenia (ITP) in refractory ITP patients and especially with Eltrombopag."
Drug Use Investigation for REVOLADE (Chronic Idiopathic Thrombocytopenic Purpura) NCT01416311	Phase not given, active not recruiting. Start date 2010, estimated completion date October 2020.

Study 200170: A Rollover Study to Provide Continued Treatment With Eltrombopag. NCT01957176	Phase IV, open label study. Active, not recruiting. Estimated enrolment: 22 (1 year and older). Start date 2013. Estimated completion date: December 2024.
LENS - Long-term Eltrombopag Observational Study - A Long Term Observational Ocular Safety Follow-up Study in Adults Who Have Received Study Medication (SB-497115-GR / Eltrombopag Olamine or Placebo) in a Phase II or III Clinical Study Evaluating Eltrombopag NCT00643929	Phase not given. Start date 2007. Completion date 2013. No results are posted on the trial record. No publication was traced.
Promacta Pregnancy Registry NCT01064336	Enrolment: 1. Start date 2010, completion date 2014. No results are posted on the trial record.
A Multicenter, Randomized, Double-Blind and Open-label Phase III Study To Compare The Efficacy And Safety Of **Eltrombopag** With Placebo In Chinese Chronic ITP Patients NCT01762761	Phase III, active not recruiting. Start date 2013, estimated completion date November 2018. Results are on the trial record.
End of EXTEND: Observing for Cure in Patients With Chronic ITP NCT01386723	Phase not given. Prospective observational study. Currently recruiting. Estimated enrolment: 20 (18 years and older). Start date 2011, estimated completion date June 2019.

5. Relevant services covered by NHS England specialised commissioning

"Ministers have agreed that the following services should no longer be commissioned by CCGs; NHS England is working to put in place arrangements to commission these services on a national basis, including ensuring that an appropriate level of resource is transferred from CCGs:

Some highly specialist adult haematology services, most likely services for patients with thrombotic thrombocytopenic purpura (the commissioning responsibility for this service will transfer between 2017 and 2019)…"